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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,554	10/04/2000	Annette Marian Doherty	5604-D1-01-TMC	1962

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	15

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/678,554	Applicant(s) DOHERTY ET AL.	
	Examiner David Lukton	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-12 and 14-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-6,9-12 and 23* is/are allowed.

6)☒ Claim(s) *14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 14 (filed 3/31/03) claims 7, 8, 13, 24, 25 have been canceled, and claims 1-6, 9-12, 14 and 19 amended. Claims 1-6, 9-12, 14-23 are pending. Applicants' arguments filed 3/31/03 have been considered and found persuasive in part. The previously imposed double patenting rejection is withdrawn, although claim 14 is now rejected as being unpatentable over claim 11 or 12 of USP 6,265,382. The rejection of claims 1-19 under 35 U.S.C. §112 second paragraph is withdrawn. The rejection of claim 19 under 35 U.S.C. 112, first paragraph is maintained. The rejection of claims 1, 2, 5, 7, 19 as anticipated by Bolton (USP 5,830,868) is withdrawn.

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Claim 14 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 11 or 12 of USP 6,265,382. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The first compound recited in (instant) claim 14 is identical to the compound recited in claim 12 of the '382 patent; the third compound recited in (instant) claim 14 is identical to the compound recited in claim 11 of the '382 patent.

In the response filed 3/31/03, it is argued that this application is a divisional of application 09/331876 (now USP USP 6,265,382), and that a double patenting rejection should not therefore be imposed. While this application has been designated a divisional of

application 09/331876, there remain two compounds in common between the (instant) application and the patent. The instant application does not fully qualify as a divisional; in any case, there remain two species in common. It is suggested that a terminal disclaimer be filed, or that the two compounds in claim 14 be deleted.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, the specification provides evidence (pp. 52-56) that the compounds of examples 1-8 exhibit some propensity to inhibit ras farnesyl transferase *in vitro*. However, this is not sufficient to enable the therapeutic method claims, or claims drawn to pharmaceutical compositions. In addition, it is not established that growth of tumor cells can be completely prevented, as asserted in claim 22, or that restenosis or psoriasis can be prevented, as asserted in claim 21. Also as indicated previously, the following references discuss the matter of various attempts by oncologists to treat cancer:

Viallet (*Lung Cancer* **15** (3) 367-73, 1996); Kemeny (*Seminars in Oncology* **21** (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* **9** (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* **127** (4) 217-25, 2001); Garattini (*European Journal of Cancer* **37** Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* **40** (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited *in vitro* activity leads to "unpredictable" results. With respect to farnesyltransferase specifically, consider the following:

- Moasser (*Breast Cancer Research and Treatment* **73** (2) 135-44, 2002) discloses (e.g., abstract) that FT inhibitor sensitivity does not correlate with the relative expression of Ras isoforms or the inhibition of Ras processing, growth factor signaling, expression of estrogen receptor or the overexpression of growth factor receptors. Also stated (last paragraph) is that Ras is not a molecular marker to guide FT inhibition therapy. This reference does not support the proposition that attempts to treat cancer patients will necessarily result in failure. However, it does support the proposition that there may be many forms of cancer which will be resistant to the effects of FT inhibition.

- Jiang (*Molecular and Cellular Biology* **20** (1) 139-48, 2000) discloses that while AKT2- transformed NIH 3T3 cells are sensitive to FTI-277, *ras*-transformed NIH 3T3 cells are not. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Prendergast (*Molecular and Cellular Biology* **14** (6) 4193-202, 1994) discloses that the FT inhibitor L-739,749 inhibited growth of ras-transformed fibroblasts. However, L-739,749 had no effect on the growth, morphology, or actin organization of v-*raf*-transformed cells. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Njoroge (*J. Med. Chem.* 40 (26) 4290-301, 1997) discloses that the Ras farnesyl-protein transferase inhibitor SCH 44342 did not show appreciable *in vivo* antitumor activity. This supports the proposition that *in vitro* activity is not

necessarily predictive of therapeutic efficacy.

- Lerner (*Oncogene* **15** (11) 1283-8, 1997) discloses that the Ftase inhibitor FTI-277 is highly effective at blocking oncogenic H-Ras but not K-Ras4B processing and signaling. The results obtained demonstrate that while FTI-277 inhibits N-Ras and H-Ras processing in the human tumor cell lines evaluated, inhibition of K-Ras processing requires both an FTase inhibitor and a GGTase I inhibitor.

- Whyte (*J Biol Chem* **272**, 14459, 1997) discloses that geranylgeranyl transferase-1 is structurally related to farnesyl transferase, and that geranylgeranyl transferase-1 may alternatively prenyl K-Ras, thereby bypassing the effect of FPTase inhibition.

- Sharma (*Annals of Oncology* **13** (7) 1067-71, 2002) discloses results of a phase II trial of SCH 66336, an FPTase inhibitor, in patients with metastatic colorectal cancer. No objective responses were observed. It is concluded that future development of this compound cannot be recommended as monotherapy in this disease.

Thus, attempts to treat cancer lead, in general, to "unpredictable" results, and conclusive evidence of efficacy of FT-ase inhibitors (to treat cancer) in humans is lacking. Even when there is an example of a compound which inhibits FT-ase, and which shows promise in humans who have a certain form of cancer, it remains to be determined which other forms of cancer will be susceptible to FT-ase inhibitors. The fact remains that the degree of inhibition varies from one compound to the next, and applicants have not determined what degree of inhibition is necessary or sufficient. Then there are the issues of bioavailability and pharmacokinetics; these parameters will vary from one compound to the next. Where cancer chemotherapy is concerned, structure/activity relationships are "unpredictable", whether FT-ase is involved or not; according, "undue experimentation" would be required

to determined which compounds (if any) will be effective, and against which forms of cancer, and under what conditions.

In the response filed 3/31/03, the following is stated:

> "Evidence of pharmacological ... activity ... will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility".

The examiner does not argue that FT-ase inhibition is irrelevant to the underlying mechanisms of tumor cell proliferation. But the question is, can one "predict" therapeutic efficacy in the treatment of a patient stricken with cancer solely on the basis of observing FT-ase inhibition *in vitro*? No such "correlation" has been established, based on the record thus far. Next, a passage from *Nelson v Bowler* has been cited (response, 3/31/03) which conveys that a showing of "pharmacological activity" constitutes evidence of a "practical utility". A passage from *Cross v Iizuka* has also been cited in defense of the proposition that a rejection of the instant claims for lack of utility would not be justified. However, no rejection for lack of utility has been imposed by the examiner. Accordingly, there is no need to discuss the question of whether a rejection for lack of utility would have been improper, had such a rejection been imposed.

Next it is argued (response, 3/31/03) that inhibition of FT-ase is an "accepted utility". As evidence, two pre-grant US patent application publications are cited. However, (a) no rejection for lack of utility has been imposed by the examiner, (b) the examiner has not

argued or implied that FT-ase inhibition is "unacceptable", and (c) the cited documents are published applications, and have not been examined.

Next it is argued (response, 3/31/03) that *in vitro* assays for FT-ase inhibition are "accepted in the art". In support of this assertion, several documents are cited. However, the examiner has never argued that *in vitro* assays for FT-ase inhibition are not "accepted". Such assays are indeed "accepted", but the question is, what conclusions can be drawn therefrom?

Next it is argued (response, 3/31/03) that the previous rejection (Office action mailed 10/1/02) (a) "called into question the acceptance of FT-ase inhibition in the art" and (b) questioned the utility of the FT-ase inhibitor R115777. However, at no point has the examiner questioned the "acceptance" of FT-ase inhibition. Rather, the question was with regard to the value of such inhibitory propensity in predicting the efficacy of a compound to successfully treat patients stricken with cancer. With regard to the second point (patentable utility), the examiner has not rejected the claims based on an assertion that they lack patentable utility. Next, the response (filed 3/31/03) offers a quote from the examiner with respect to an article which had been cited in an earlier response (response filed 4/3/02). The article in question was Sharma (*Oncologist* **5** (2) 99-107, 2000). Sharma was cited by applicants (response filed 4/3/02) in response to a rejection under 35 USC §112, first paragraph in the Office action mailed 1/2/02. The comment by the examiner (Office

action mailed 10/1/02) was simply that Sharma had provided no evidence of therapeutic efficacy of the compound designated as R115777. The observation by the examiner that Sharma had provided no evidence of therapeutic efficacy of R115777 does not mean that the claims are, or should be rejected for lack of patentable utility. The point is just that, whatever the merits of Sharma (*Oncologist* **5** (2) 99-107, 2000), this article does not support the proposition that FT-ase inhibition in vitro is predictive of efficacy in the treatment of cancer in humans or other mammals.

Next, the response (filed 3/31/03) points to Norman (*Curr Opinion Invest Drugs* 3, 313-319, 2002) which discloses (page 315, col 1) that the FT-ase inhibitor tipifarnib is undergoing phase III trials for pancreatic cancer and leukemia "but no results have yet been reported". In addition, in the second paragraph of the abstract, it is asserted that an investment banking firm made a prediction in November of 2001 that a "new drug application" would eventually be filed by Janssen Pharmaceuticals. Whether such an application has been filed with the appropriate authorities is not made clear. However, there is nothing in the article (Norman, 2002) which shows that tipifarnib is effective to treat cancer or leukemia in humans. Furthermore, this article does not represent the "state of the art" at the time of the invention (4/11/97).

In accordance with the foregoing, neither the specification nor subsequently filed documents provide evidence that, at the time of the invention, the skilled artisan would have

believed that a correlation existed between the propensity of a compound to inhibit FT-ase, and the efficacy of the compound in treating humans stricken with cancer. In addition, there are several references (cited by the examiner) which support the conclusion that attempts to treat cancer in humans using FT-ase inhibitors will lead to "unpredictable" results. In the response filed 3/31/03, no explanation is offered as to why this conclusion (of unpredictability) might not be valid. Accordingly, the examiner continues to argue that therapeutic intervention using FT-ase inhibitors will produce unpredictable results; taken together with the absence of any working examples showing such therapeutic efficacy, and in view of the state of the art (with regard to cancer treatment) at the time of the invention, the skilled artisan would conclude that "undue experimentation" would be required to practice the claimed invention.

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Claim 19 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is rendered indefinite as to the objective(s) of the "therapeutic efficacy".

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 5/19/03

Christopher S. F. Low

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